REMARKS

In this non-final Official Action, the Examiners have taken the following formal positions:

(i). The Examiners have found applicants' Provisional Election with Traverse of Group I to be persuasive; and have rejoined Groups I and II and all of original claims 1-17 respectively as a single invention for prosecution in the instant application.

(ii). The Examiners have objected to the figures of the Drawing as failing to comply with the requirements of 37 C.F.R. 1.84 (p)(5).

(iii). The Examiners have found that the applications fails to comply with the requirements of 37 C.F.R. 1.821-1/825 concerning sequence listings for specific amino acid segments.

(iv). The Examiners have objected to original claims 12, 13 and 14 respectively as being of improper dependent form for failing to further limit the subject matter of a previous claim.

(v). The Examiners have rejected original claims 1-17 under the judicially created doctrine of obviousness-type double patenting over the claims of co-pending USSN 09/855,468.

(vi). The Examiners have rejected original claims 1-14 under 35 U.S.C. 112, first paragraph, as requiring a formal deposit of the cells under the terms of the Budapest Treaty.

(vii). The Examiners have rejected original claims 1-14 under 35 U.S.C. 112, first paragraph, not being enabled by the disclosure of the Specification text for any microglia cell line other than a genetically modified microglia cell line.

(viii). The Examiners have rejected pending claims 15-17 respectively under 35 U.S.C. 103(a) as being unpatentable over the Janabi *et al.* 1996 article and the Briers *et al.* 1994 publication in view of the Gage *et al.* patent reference [U.S. Patent No. 5,762,926].

In response, applicant has amended the language of claims 1, 12-14 and 15 respectively; added new claims 18 and 19 respectively; and submits herewith the documentary and CRF diskette sequence listings required for nucleic acid and amino acid sequences. By these claim amendments, newly added claims, enclosures, and the discussion presented hereinafter, applicant believes he has overcome and obviated each basis for objection and rejection stated by the Examiners in the instant Official Action.

It is also applicant's purpose and desire to advance the prosecution of the present application substantively and meaningfully in the most expeditious manner possible. However, effective patent prosecution requires that applicant's undersigned attorney not merely acknowledge the Examiners' stated bases for objection and rejection, but rather present and advocate different, alternative, and often antagonistic views, positions, facts,

and points of law which frequently stand in opposition to and often are in conflict with the Examiners' given stance. It is therefore hoped and believed that all of the remarks and statements presented hereinafter will be seen as proper and objective attempts by applicant's undersigned attorney to persuade the Examiners to recognize and accept a different point of view and alternative conclusion; and that none of the comments, explanations and/or criticisms presented hereinafter are directed at the Examiners' status, personality, or professionalism.

Initially, several preliminary matters require attention and are therefore addressed first. These preliminary matter are individually discussed below.

I. Preliminary Matters

A. The Examiners' Formal Withdrawl Of The Restriction Requirement

The Examiners of record have found applicant's Provisional Election with Traverse to prosecute Group I to be persuasive; and, in consequence, have formally rejoined all of the original claims [Nos. 1-17 respectively] as the defined invention to be substantively reviewed and evaluated on the merits in this application. Applicant and his undersigned attorney deeply appreciate the Examiners' reconsideration and their formal withdrawl of the earlier-imposed Restriction Requirement.

B. The Examiners' Objection To The Drawing

The Examiner's objection to the Drawing seem to be based upon the allegations that: (1) some as yet unspecified reference signs are not mentioned in the description; (2) the components of Figs. 2, 3, 4 and 6 respectively are not explained in the Specification; and (3) the reference signs for Fig. 6 contains five components [A-E] which are not mentioned in the description.

However, applicant and his undersigned attorney contend that the Examiners' allegations as stated do not appear to have a substantive basis of support. To evidence and prove applicant's position, the attention of the Examiners is therefore directed to the following points of information in the Specification text.

The components of Figs. 2, 3, 4 and 6 are first set forth explicitly at Page 6, lines 9-22 and Page 7, lines 1-5 respectively of the Specification text. The brief descriptions as stated individually for Figs. 2A-2D, Figs. 3A-3B, and Figs. 4A-4B are correct; and the inadvertent typographical error originally at Page 7, line 1 for the brief description of Fig. 6 has been presently amended in accordance with 37 C.F.R. 1.121 to now recite "Figs. 6A-6E".

In addition, the Specification also identifies and describes each of these figures individually and in far greater detail within the appropriate portions of

the Specification text - that is, within the disclosure of the experiments performed and the empirical data recorded by applicant. Thus, Figs. 2A-2D are further described properly and in full at Page 31, lines 18-22 and at Page 32, lines 1-15 respectively; Figs. 3A and 3B are additionally described in detail at Page 35, lines 7-19 respectively; Figs. 4A and 4B are further described in proper detail at Page 35, lines 20-23 and Page 1-18 respectively; and Figs. 6A-6E are described completely and in full at Page 37, lines 21-24 and at Page 39, lines 1-8 respectively.

By this totality of descriptive text within the Specification as a whole, applicant respectfully submits that each of the Examiners' alleged deficiencies concerning the Drawing are substantially unsupported; and that - contrary to the Examiners' stated views - the Specification text fully discloses and properly describes each of the reference signs for all the figures constituting the Drawing as a whole in a manner which complies with and satisfies the requirements of 37 C.F.R. 1.84(p)(5). For these reasons, applicant respectfully requests that the Examiners reconsider their stated position and withdraw this ground of objection against the Drawing of the instant application.

C. Applicant's Submission Of Sequence Listings In Compliance With 37 C.F.R. 1.821-1.825

The Examiner has stated that applicants' previous documentary and

CRF submissions have failed to include all the nucleic acid sequences as found at Pages 27-29 as well as the amino acid sequence as stated at Page 31, line 4 of the Specification text; and therefore have failed to comply with the standards for patent applications containing nucleic acid and/or amino acid sequences, as required by 37 C.F.R. 1.821-1.825.

Applicant, via his undersigned attorney, has reviewed the substance of his initial submission of sequence listing documents and CRF diskette as mailed March 14th, 2003; and acknowledges the essential facts as stated by the Examiners. For these reasons also, applicant now presents and encloses a second documentary and second CRF diskette submission, in fulfillment and compliance with the sequence rules 37 C.F.R. 1.821 - 1.825; and which lists and identifies all the nucleic acid sequences at Pages 27-29 as well as the amino acid sequence appearing at Page 31, line 4. This second sequence listing documentary and CRF diskette submission is enclosed herewith in support of this Response.

Accordingly, as a consequence of this enclosed second submission, applicant therefore respectfully requests the Examiners to reconsider their stated position; and to withdraw this reqirement against the instant application.

D. The Examiners' Objection to Some Of The Original Claims

The Examiners have objected to the wording of original claims 12, 13, and 14 respectively as being of improper dependent form for failing to limit further the subject matter of a previous claim. Unfortunately, the basis of the Examiners' objection appears to be incorrect and erroneous.

The Examiners have noted that claims 12-14 are dependent claims which depend from independent Claim 1, a composition of matter definition. However, the Examiners apparently have failed either to recognize that the composition of matter has a well described legal utility; or to appreciate that dependent claims 12-14 merely recite in greater detail the described utility of the subject matter as a whole comprising the present invention - a utility which is clearly, fully and adequately disclosed by the Specification text at Pages 18-21 respectively.

Original Claims 12-14 respectively thus positively recite and restate the substantive utility provided by the composition of independent Claim 1; and merely delineate the described utility of the invention under particular use circumstances, such as some expected and intended in-vitro and in-vivo applications. The Examiners will also take note that a detailed and particular recitation of the disclosed utility for a claimed composition of matter - when presented in the form of a dependent claim - is both legally proper as a further limitation of a broadly claimed invention and is an acceptable form of

claim definition and presentation long-established as black letter law.

The given language of original Claims 12-14 specifying the utility of the invention under particular use circumstances, however, can often be improved. For purposes of clarification, therefore, new dependent Claims 18 and 19 have been added which recite "in-vitro" and "in-vivo" wording and delineate use applications generally; and Claims 12, 13 and 14 respectively have been amended to depend from either Claim 18 or 19 in order to specify and further limit the recognized utility of applicant's defined invention under particular in-vitro and particular in-vivo use circumstances.

By these claim amendments therefore, applicant respectfully submits that the requirements of 37 C.F.R. 1.75(c) have been fully met and satisfied. Accordingly, applicant respectfully requests that the Examiners reconsider their stated position and withdraw this ground of objection against the presently pending claims.

Applicant will now address each of the different substantive bases for rejection stated by the Examiners in the instant Official Action with regard both to the pertinent legal requirements and the relevant factual circumstances. Yet, since so much of the Examiners' stated views and positions are dependent upon having a focused and clear understanding of what applicant's invention truly is - as defined by the language of the

presently pending claims, applicant deems it both useful and appropriate to review summarily here the subject matter as a whole which is applicant's claimed invention.

II. Applicants' Claimed Invention

Applicants' invention is claimed most broadly by amended independent claims 1 and 15 respectively. Amended independent Claim 1 recites a genetically modified human microglia cell as a composition of matter definition. Thus, Claim 1 defines a discrete human microglia cell which has been genetically modified by human intervention; is stable as a genetically modified human cell; and can be maintained in-vitro as a stable and substantially homogeneous microglia cell line of human origin.

It will be appreciated also that amended independent Claim 1 recites a series of specific elements and limitations for the human microglia cell composition of matter as singular properties, capabilities and functions; explicitly states that the genetically modified human microglia cell is stable after its generation as a genetically altered living cell; and provides an altered human cell which is capable of being maintained in vitro as a substantially homogeneous cell line. All of these cell traits and capabilities are disclosed in full by the Specification text.

In comparison, amended independent Claim 15 defines a method for transforming human microglial cells into an immortalized cell line of genetically modified human microglia cells which can then be expanded and maintained as an immortalized and substantially homogeneous cell line in-vitro. The manipulative steps of Claim 15 are explicitly identified, unambiguously described, and clearly delineated, both individually and with respect to each other, by the disclosure of the Specification text

Also, it will be recognized that the Specification text not only describes in detail the commonly shared characteristics and properties for the immortalized and substantially homogeneous human microglia cell at pages 12-17 respectively; but also sets forth descriptive details and preferred method of making the genetically modified human microglia cell via the experiments and empirical data disclosed at pages 21-42 respectively. The Examiners' attention is directed in particular to the detailed recitation and description of the methods and materials which allow any ordinarily skilled person to make and use the genetically modified human microglia cells as set forth at Page 21, line 20 through Page 31, line 14. The probative experiments and empirical data demonstrating the attributes, properties, activity and function of these genetically altered cells are full and completely disclosed at Page 31, line 16 through Page 42, line 2 of the Specification.

Thus, as a result and consequence of the broad, explicit and complete disclosure of the genetically modified human microglia cell as well as the mode and manner of its generation and maintenance as a stable immortalized human cell line in-vitro, amended independent claims 1 and 15 merely state and set forth the specific characteristics and particular properties commonly shared among all the embodiments broadly and described in great detail by the Specification text.

Moreover, amended independent Claims 1 and 15 individually delineate a human microglia cell family membership which is unique in all its potential embodiments; is readily distinguishable from other kinds of immortalized human cells; and constitutes a stable and substantially homogeneous family of human microglia cells which have been similarly genetically altered, are characteristically and functionally alike, and constitute progeny cells which all share and originate from a single common source.

One other point of difference must also be discussed. It will be recognized that the word "therapeutic" is completely absent and is not recited by any language actually employed in the presently pending claims. Moreover, since applicants' invention is set forth in the alternative only as a cell composition of matter definition and as a method for transforming human microglia cells into a genetically modified cell line, the recited composition elements and manipulative steps of the method comprising the invention as a

whole are not and cannot be said to define any "therapeutic treatment" as such. Instead, the broad utility disclosed by the Specification text for the claimed invention is overtly and expressly recited by newly added dependent claims 18 and 19 respectively, while dependent claims 12-14 respectively have been amended to recite application particulars and limitations for the disclosed utility.

III. The Rejection Based Upon Obvious-Type Double Patenting

The Examiners have provisionally rejected Claims 1-17 respectively under the judicially created doctrine of obvious-type double patenting as being unpatentable over the claims of co-pending USSN 09/855,468.

The legally required underpinnings to support such a rejection basis are three: (1) at least one person must be commonly named as an inventor in both the instant application and USSN 09/855,468; (2) the instant application and USSN 09/855,468 be co-pending; and (3) the claims of the instant application and those of USSN 09/855,468 are not patentably distinct from each other.

Clearly, the Examiners have presented this basis of rejection in good faith; but more recent events have overtaken and altered the factual basis and underlying presumptions upon which this obvious-type double patenting rejection was made.

The attention of the Examiners is directed to the current status of USSN 09/855,468 filed May 5, 2001. This patent application, USSN 09/855,468, has become and remains today legally abandoned, owing to applicant's failure to file timely a proper reply to the Office Letter mailed on January 30, 2003. In addition, a formal Notice Of Abandonment for USSN 09/855,468 [signed by Gary Kunz, SPE] was mailed on August 26, 2003; and the abandonment status formally confirmed by telephone subsequently on August 20, 2003 by Examiner Christopher Nichols. Thus, USSN 09/855,468 is today no longer an active or pending patent application; and therefore cannot be said to be co-pending presently with the instant application.

The overall result and consequence of the current abandonment status for USSN 09/855,468 is that the requisite minimal underpinnings necessary for the obviousness-type double patenting rejection no longer factually exist. There is no co-pendency today between the instant application and USSN 09/855,468; and, accordingly, there is no longer any underlying legal basis for a rejection based on obviousness-type double patenting.

For these reasons, applicant respectfully requests that the Examiners reconsider their stated position and withdraw this ground of rejection against the claims of the instant application.

IV. The Rejection Under 35 U.S.C. 112, 1st Paragraph; A Deposit Of Living Materials Is Necessary For Enablement

A basis of rejection and one issue in controversy stated in the instant Official Action is the Examiners' determination that the subject matter of applicant's invention is not enabled by the Specification in such a way as to allow the public to make and use applicant's claimed invention. The underlying substance of this legal basis of rejection is focused upon the answer to a single factual question: Does the public have the ability to obtain the necessary living materials and to make and use applicant's invention as described and claimed when such capability is based solely upon the quality and quantity of information and knowledge provided by the disclosure of the Specification text as a whole to a person of ordinary skill in this technical field?

Unfortunately, the Examiners have not spoken to the essential and central question Instead, the Examiners' given statement is merely "...The specification does not disclose a repeatable process to obtain the cell lines and it is not apparent if the cell lines are readily available to the public...."[Page 5, paragraph 10 of the instant Official Action].

Applicant also notes that: no facts are given by the Examiners as to how or why the disclosed process to obtain the cell lines is said not to be repeatable; nor is there any explanation provided as to the basis upon which the Examiners decided that the totality of the disclosure in the Specification

did not provide sufficient information and knowledge to the reader about the process to obtain the cell lines such that the method is repeatable; nor is there any justification given by the Examiners, either legally or factually, for their stated view and conclusion.

In sum and substance, the Examiners have taken the view and position that the living material, cell characteristics, and cell features and properties constituting a genetically modified human microglia cell in general and the HM06 cell line in particular - which the Specification text describes in great detail both as a preparation method (defined by independent claim 15) and as a genetically altered cellular material having a viral vector and exogenous DNA encoding a specific protein product and which can be maintained as a stable cell line in-vitro (defined by independent Claim 1) - cannot be reproduced or obtained by the scientific and technically versed community at large because they cannot obtain the necessary living materials. Moreover, in the Examiners' expressly stated view, the HM06 cell line, a preferred embodiment of the genetically modified human microglia cells, despite being disclosed in full as well as being experimentally described and empirically evaluated within the written description of the Specification text, are deemed by the Examiners to be insufficient for enablement purposes - unless and until a deposit of the HM06 cell line itself is made of record under the Budapest Treaty with a publically accessible cell repository.

Unfortunately, the Examiners have not properly considered the legal basis necessary before imposing a deposit requirement; nor have the Examiners considered the underlying the quality and quantity of facts, technical information and scientific details, performed experiments and reported empirical data actually provided by the disclosure of the instant Specification in their stated grounds for rejection.

For these reasons, applicants therefore present a proper summary of the true legal requirements and factual underpinnings necessary for a deposit requirement to be imposed, as established by the pertinent case law decisions to date.

1. It is a legal axiom and a first principle that the language of the claim defines the scope of the invention [Yale Lock Mfg. Co. V. Greenleaf, 117 U.S. 554 at 559 (U.S. Sup. Ct. 1886)]. Moreover, while the invention may be illustrated by the disclosure and description of the Specification text, the nature, scope and definition of applicants' invention is focused upon and limited to only the wording actually recited by the claim. Thus, no person can either broaden or narrow the claim wording to introduce or yield something different than what the language of the claim sets forth itself [Continental Paper Bag Co. V. Eastern Paper Bag Co., 210 U.S. 405 at 419 (U.S. Sup Ct. 1908); Cimiotti Unhairing Co. v. American Fur Ref. Co., 198 U.S. 399 at 410 (U.S. Sup. Ct. 1905); Autogiro Co. Of Am. v. United States,

155 U.S.P.Q. 697 at 701 (Ct. Cl. 1967)].

2. The pertaining legal requirement of 35 U.S.C. 112, 1st paragraph, is that the written text of the Specification as a whole provide sufficient information, full and adequate description, and complete details such that the reader of the disclosure will be able to make and use the invention as claimed without undue experimentation [In re Wands, 8 USPQ2d 1400, at 1402-1403 (Fed. Cir. 1988)]. All that enablement legally requires, therefore, is that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provide by the Specification text. Moreover, nothing more than objective enablement is legally required: It is therefore irrelevant whether the teaching is provide through a broadly written description, or through exemplary illustrations and technical details, or through actual scientific experiments and observed empirical data [In re Vaeck, 20 USPQ2d 1438 at 1444 (Fed. Cir. 1991); In re Wright, 27 USPQ2d 1510 at 1513 (Fed. Cir. 1993)].

3. However, where an invention depends on the use of living materials, such as microorganisms or cultured cells, it MAY be impossible to enable the public to make and use the claimed invention (*i.e.,* to obtain the living materials) solely by means of reading the written disclosure of the Specification. In such factual instances - *i.e.,* where the public cannot obtain the living materials solely by means of reading the disclosure of the

Specification - a legal mechanism has been developed for complying with the enablement requirement by depositing the living materials in a public cell depository, which will subsequently distribute samples of the living material to the public who wish to practice the invention after the patent issues [In re Argoudelis, 168 USPQ 99 at 101-102 (CCPA 1970)].

4. Nevertheless, a deposit requirement may be imposed only after a factual evaluation and determination has been completed; and the determination has shown on reasonable grounds that it is factually impossible for the public to make the invention, owing to their inability to obtain the living materials despite having knowledge of all the information, knowledge, descriptive details and insights provide by the disclosure of the Specification text as a whole. Thus, the factual evaluation and determination must precede any imposed requirement for making a deposit of living materials. Equally important, the requirements and purposes of enablement can be legally met and satisfied in ways other than by making a formal deposit of living material with a public cell depository [In re Lundak, 227 USPQ 90 at 95-96 (Fed. Cir. 1985); In re Wands, 8 USPQ2d at 1403 (Fed. Cir. 1988)].

5. If and when the Examiners reject one or more claims because of the enablement requirement of Section 112, the Examiners bear the initial burden of setting forth a *prima facie* case and providing a reasonable

explanation as to why they believe that claim is not adequately enabled by the description of the invention provided by the totality of information disclosed within the Specification text of the application. The Examiners are therefore legally required and obligated to present sufficient facts, proper reasoning and probative evidence about the objective truth of the information presented within the Specification text; to explain why the Examiners doubt the truth or accuracy of any statement in the disclosure of the Specification (especially about whether or not there is disclosed a repeatable process to obtain the cell line); and to back up such assertions with acceptable evidence or reasoning which is inconsistent with the information or statements disclosed by the Specification text.

It is thus incumbent on the Examiners to establish first a *prima facie* case of non-enablement, particularly where the Examiners demand that a deposit be made by applicant in order to legal comply with the enablement legal requirement. A mere statement, or opinion, or point of view by the Examiners that they individually believe that the disclosure is not enabling of itself or is insufficient to support one or more specific claims is not legally adequate or proper to meet the burden of presenting and supporting a *prima facie* case of non-enablement [In re Marzocchi, 169 U.S.P.Q. 369 (CCPA 1971); In re Sichert, 196 U.S.P. Q. 209 (CCPA 1977)].

Applicant and his undersigned attorney therefore respectfully submit that the Examiners unfortunately have:

(i) failed to establish a *prima facie* case of non-enablement which is their primary legal duty;

(ii) failed to consider properly the legal basis necessary before imposing a deposit requirement;

(iii) failed to consider the underlying the quality and quantity of facts, technical information and scientific details, performed experiments and reported empirical data actually provided by the disclosure of the instant Specification;

(iv) failed to recognize that the totality of information and knowledge provided by the disclosure of the Specification to the person ordinarily skilled in this technical field in fact provides a repeatable method for obtaining the novel cell line; and

(v) failed to consider whether or not the written text of the Specification as a whole provides sufficient information, full and adequate description, and complete details such that the reader of the disclosure will be able repeatedly to prepare the living materials and to make and use applicant's invention as claimed.

Accordingly, for all these reasons, applicant respectfully submits and affirms that the Examiners have made multiple prejudicial errors of law and

fact; and requests that they should reconsider their stated position and withdraw this ground for rejection and the requirement for a deposit against the presently pending claims.

V. The Rejection Under 35 U.S.C. 112, 1st Paragraph; Non-Enablement

The Examiners have rejected original claims 1-14 respectively under 35 U.S.C. 112, first paragraph, as allegedly failing to provide information sufficient to enable one skilled in the art to make and practice applicants' invention as claimed. The Examiners have presented their views and position at pages 4-8 in the instant Official Action. The essence of their stated rationale is as follows:

> "The above invention is drawn to a microglia cell line with intended uses of screening, treatments for neurodegeneration, and treatments of pathologies. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification teaches a method of isolating and genetically modifying the cells *in vitro*. However, no reproducible method of making a microglia cell line with all the characteristics as defined by claim 1-12 is presented." [Page 7, paragraph 15 of the instant Official Action].

In response to the Examiners' stated rationale, applicants and their undersigned attorney respectfully submit:

First, the Examiners have employed legal standards which are subjective and do not conform to the correct and proper objective legal standards regarding adequacy of disclosure for enablement as prescribed by

statute and the governing caselaw decisions;

Second, the Examiners have failed to appreciate properly the totality of factual content disclosed by the Specification text and have failed to give proper credence to the quality and quantity of the detailed information presented by the written disclosure; and

Third, the Examiners have reviewed the pending claims and the Specification text from an erroneous perspective and from a vantage point which fails to recognize or take into account the ordinary skills and commonplace knowledge currently available and conventionally employed in the relevant field.

Each of these major failures and errors will be demonstrated and explained in detail.

The legal errors of the Examiners:

Applicant respectfully submits that the Examiners have inadvertently and unfortunately departed from the proper legal standards and requirements of enablement; and presented applicants instead with a subjective view and improvised position which is flawed, erroneous and legally unsupportable. Applicant therefore offers the Examiners a true and correct statement of the objective legal standards by which sufficiency of enablement is to be determined.

1. Nothing more than objective enablement is required as a matter of

law; and it is irrelevant whether this quantum of information is provided through a broadly written description and disclosure, or by illustrative examples, or by working experiments with observed empirical data [In re Wright, 27 U.S.P.Q. 2d 1510 (1993)]. Thus, there is no meaningful difference when determining the adequacy of description and information for enablement purposes whether a broadly written description in meaningful detail is provided by a Specification text; or if a series of illustrative hypothetical examples is provided in a variety of circumstances; or if a series of actual experiments with resulting empirical data and conclusions supported by the empirical data is present in any degree, quality or form. Any presentation of such information in any of these formats is legally and factually sufficient to satisfy the enablement requirement.

2. If and when the Examiners reject one or more claims because of the enablement requirement of Section 112, the Examiners bear the initial burden of setting forth a *prima facie* case and a reasonable explanation as to why they believe that the scope of protection defined by that claim is not adequately enabled by the description of the invention provided by the totality of information disclosed within the Specification text of the application. The Examiners are thus legally required and obligated to present sufficient fact, reasoning and evidence about the objective truth of the information presented within the Specification text; to explain why the

Examiners doubt the truth or accuracy of any statement in the disclosure of the Specification; and to back up such assertions with acceptable evidence or reasoning which is inconsistent with the information or statements disclosed by the Specification text.

It is thus incumbent on the Examiners to establish first a *prima facie* case of non-enablement. A mere statement, or opinion, or point of view by the Examiners that they personally believe that the disclosure is not enabling of itself or is insufficient to support one or more specific claims is not legally adequate or proper to meet the burden of presenting and supporting a *prima facie* case of non-enablement [In re Marzocchi, 169 U.S.P.Q. 369 (CCPA 1971); In re Sichert, 196 U.S.P. Q. 209 (CCPA 1977)].

3. It has been emphasized repeatedly by major caselaw decisions that the enablement requirement of Section 112, 1st paragraph does not require a specific example of everything possible within the scope of a broadly defined claim [In re Anderson, 176 U.S.P.Q. 331 (CCPA 1973)]; and that not even one single specific illustrative working example need be present within the disclosure of a specification text in order to meet and satisfy the enablement requirement of Section 112 [In re Stephens, 188 U.S.P.Q. 659 (CCPA 1976)].

Moreover, the fact that a Specification text may be devoid of even one working or illustrative example is itself without legal significance; it is well

established that illustrative examples or empirical data and the like are not legally necessary in order to have an enabling disclosure [In re Borkowski, 164 U.S.P.Q. 642 (CCPA 1970)]. Accordingly, the presence or absence of even a single illustrative or working example does not of itself provide any legal basis or support to explain why a Specification text is not enabling or to explain why the scope of the enablement is not commensurate with the scope of protection sought by the pending claims.

4. As a matter of long-established legal principle, there is no requirement under 35 U.S.C. 112, 1st paragraph that an inventor correctly set forth, or even know, how or why the claimed invention works or functions [Newman v. Quigg, 11 U.S.P.Q.2d 1340 (Fed. Cir. 1989)]. Moreover, it is axiomatic that an inventor need not even comprehend the scientific principles upon which the practical effectiveness of his invention rests [Fromson v. Advance Offset Plate, Inc., 219 U.S.P.Q.2d 1137 (Fed. Cir. 1983)]. Accordingly, therefore, no legal basis or duty of any kind exists for the written disclosure of a Specification to provide any explanation, or any understanding, or even any theory of why the claimed invention works or how the claimed invention functions.

Furthermore, the presence of experimental details or other descriptive statements within a disclosure that a particular physiological phenomenon was observed and experimentally evaluated are not deemed to be

"intrinsically suspect" or "unpredictable" simply because the underlying biomolecular basis for the empirical observation cannot be predicted or explained [In re Cortright, 49 U.S. P.Q.2d 1464 (Fed. Cir. 1999)]. Thus, the Examiners cannot overtly state or even suggest that the enablement requirement legally demands that applicants prove the mechanism of action involved; or explain the nature of a function/structure relationship to account for an observed physiological activity; or demonstrate the "efficacy" of the consequential result caused by a genetically modified human microglia cell line.

5. The enablement requirement of Section 112, 1st paragraph, also does not require that the disclosure of the Specification convince any person (including the Examiners) that the assertions, information, and knowledge contained therein are proven correct to the point of absolute certainty [In re Robins, 429 F.2d 452 (CCPA 1970)]. There is thus no legal requirement in law that the Examiners become completely persuaded; or become a committed follower; or be a true supporter of the scientific model, theory or premise upon which an invention is based or of any mechanism of action upon which the invention relies.

Rather, the legal obligation and burden upon the Examiners is a quite different one entirely: the Examiners are required to evaluate the totality of the disclosure within the Specification text when evaluating whether the

disclosure is adequate for purposes of enablement; and the purpose of the Examiners' evaluation is to determine objectively whether there is sufficient information, detail and knowledge disclosed within that text which would allow a person of ordinary skill in the pertinent art to make and use the invention as claimed.

6. It has long been recognized that the Examiners are neither permitted to act as nor intended to be either a scientific board of inquiry or an editorial review committee. Also, the purview of the Examiners' objective assessment is not intended or expected to delve into the details or minutiae which further experimentation or other additional empirical data might reveal or supply in terms of a greater appreciation of what the invention is and/or what might be the most optimal conditions of how the invention is to be practiced [In re Marzocchi, 169 U.S.P.Q. 367 (CCPA 1971); In re Brana, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995)].

Moreover, where the Examiners have expressed subjective doubt and personal opinion regarding the nature of the invention, or the range of specific embodiments, or the number of illustrative examples embodying the invention, or the expected efficacy in vivo of a microglia cell line prepared in vitro - rather than objectively address and evaluate whether the totality of the Specification text provides adequate information as to how to make and use the invention as claimed – such a rejection is then without factual or

legal support and is completely improper [In re Armbruster, 185, U.S.P.Q. 152 (CCPA 1975)].

7. Enablement is also legally satisfied and fulfilled when one possessed of the knowledge and information provided by the Specification text could use the invention as claimed without undue experimentation [In re Eynde, 178 U.S.P.Q. 470 (CCPA 1973)]. The objective determination of what constitutes "undue experimentation" in any given instance requires the application of the standard of reasonableness, having due regard for the nature of the invention as claimed and the state of the pertinent art. This test is not merely quantitative since a considerable amount of experimentation is legally permissible. Thus, if such experimentation is merely routine or if the Specification text provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed, then such experimentation is not "undue". The key and essential word, therefore, is always "undue" and not "experimentation" [In re Angstadt, 190 U.S.P.Q. 214 (CCPA 1976); Atlas Powder Company vs. E.I. DuPont DeNemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984); In re Wands, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988)].

8. In addition, the mere possibility that a recited claim might include a large

number of embodiments and use instances does not of itself prevent or

legally deny the allowance of claims having a broad scope. Moreover, it is not incumbent on an applicant who has made a broad invention either to demonstrate with evidence or to prove with data (I) empirical support for the entire descriptive range of possibilities envisioned; or (ii) the degree of embodiment variation or the diversity of capabilities in every embodiment and use instance of the invention which may fall within the broad scope of the claims. The function of a recited claim is to point out what the invention is and to define the scope of the protection; it is not, however, intended to exclude conditions or instances which are possibly of no use in practicing the invention [In re Sarett, 327 F. 2d 1005 (CCPA 1964)].

Thus, when the degree of experimentation involved is commonplace, such as the personal selection of commonly available choices known in the field or which become available via a study of other routine parameters and variations that anyone ordinarily skilled in the pertinent art might expect, none of these experiments are "undue"; and the Specification disclosure, as written, is legally adequate and factually sufficient to satisfy the enablement requirement [In re Geerdes, 180 U.S.P.Q. 789 (CCPA 1974); In re Morehouse, 545 F.2d 162 (CCPA 1976)].

The factual errors of the Examiners:

As applicants have shown and documented previously herein, the

Specification text describes in detail ALL of the following:

(a) A preferred method for producing immortalized human microglia cells and a stable cell line is presented at Page 7 line 18 through Page 12, line 5 of the Specification. Included are information concerning vectors, general method of preparation, the human microglia cell culture, retrovirus-media gene transfer techniques, and the cell transfection process.

(b) The characteristics and properties of immortalized genetically modified human microglia cells and the HM06 cell line is presented at Page 12, line 7 through Page 17 of the Specification. Included is a detailed technical description of surface antigens, cell type-specific markers for central nervous system cells, the phagocytic capacity of the cells, the chemkine and cytokine expression of the cells, an analysis of non-stimulated HM06 cells, and an analysis of agent stimulated HM06 cells.

(c) A written description in detail of the expected and intended in-vitro assay uses and in-vivo therapeutic uses for the immortalized human microglia cells is given at Page 18, line 1 through Page 21, line 9 of the Specification. A variety of illustrative examples and intended uses for both in-vitro and in-vivo applications is provided.

(d) A presentation of actual experiments performed and empirical data recorded is stated at Page 21, line 11 through Page 39, line 20. A complete recitation of the commonly available starting materials and a preferred

method for preparation of genetically modified cells is provided. The detailed information and knowledge given in the text includes the chosen reagents, the primary microglia cell culture, the retrovirus-mediated gene transfer technique, the methods for characterization of genetically modified HM06 cells, the sequences of PCR primers for sense and antisense nucleic acids, and the ELISA analysis of gene expression products. The experimental series describes the method for isolating human microglia cell lines, the characterization of the HM06 human microglia cell line, the calcium influx of HM06 cells following exposure to ATP, a characterization with RT-PCR analytical techniques, the expression of cytokines and chemokines, and the effects of β-amyloid.

(e) A statement of conclusions based upon empirical results is presented at Page 40, line 1 through Page 42, line 2 of the Specification. The recited conclusions based on empirical data provide additional guidance, further insights and proper perspective for the person ordinarily skilled in this technical field.

Applicant also notes that the commonly shared characteristics and properties of the genetically modified human microglia cell family are thus set forth in exquisite scientific detail; and a description and explanation of the expected and intended in-vitro and in-vivo capabilities, uses and applications is given to the reader in a full and complete presentation.

In addition, the commonly shared characteristics and properties of the genetically modified human microglia cell and stable cell line is illustrated by example, by analytic evaluation, by surface markers, and by cell properties. It will be noted that the markers, attributes, properties and characteristics are overtly stated and individually set forth; and this antecedent description corresponds and directly correlates with the requisite elements and specific limitations recited by the presently pending claims.

Equally important, in direct opposition and contradiction to the Examiners' stated view, these specified traits and attributes for the human microglia cell line and the HM06 cells in particular have been experimentally illustrated and empirically validated within the Specification. These are working examples and representative embodiments which provide ample evidence and empirically demonstrate the requisite structure, function, and properties for the genetically modified human microglia cell family as defined by independent claims 1 and 15 respectively.

It must be recognized and acknowledged also that the Specification text does overtly disclose a reproducible method of making a microglia cell line having all the characteristics defined by the presently pending claims within the Specification text. A recitation of the attributes, properties and functions of the human microglia cell is given repeatedly and in complete detail; and the written disclosure provides a full and complete recitation and

review of the traits and capabilities of the HM06 cell line as merely one preferred embodiment of all genetically altered human microglia cells generally. The quantity and quality of such information clearly demonstrates and exemplifies the value and capabilities of the subject matter as a whole which is applicant's defined invention.

Applicant and his undersigned attorney therefore respectfully submit and affirm that an objective review and earnest evaluation of the written description and the variety of illustrative details disclosed by the Specification text reveals all the necessary knowledge and information concerning the structure, attributes and traits of the genetically modified human microglia cell (defined by independent Claim 1) as well as of the method for making such cells (defined by Claim 15) - such that any ordinarily skilled practitioner working in this technical field could identify, prepare and use any chosen member of the human microglia cell family.

The prejudicial error in the Examiners' evaluation:

1. Applicant and his undersigned attorney find that the Examiners' views and positions as stated within the instant Official Action, merely represent the Examiners' subjective desire for recitations of non-essential technical details and information; and, in addition, constitute a wish for a incidental and optional information which can be experimentally obtained at

will and without major difficulty by persons ordinary skilled in this art – after having read the broad and detailed description provided by the Specification text.

Applicant and his undersigned attorney also submit and affirm that no legal justification or support exists in law for the Examiners' stated demand that an " in-vivo therapeutic" activity or relationship be disclosed; and maintain that an enabling disclosure – as revealed by the controlling caselaw decisions - does not demand or legally require any description or inclusion of an " in-vivo therapeutic" treatment methodology as such be disclosed within the Specification text in order to meet and satisfy the 1st paragraph of Section 112.

Moreover, by making such a demand and posing the demand as a legal requirement which must ostensibly be satisfied for enablement purposes, the Examiners have unknowingly committed gross and prejudicial legal error. Applicant affirms that the Examiners are without legal support, or proper cause, or lawful justification for their stated view and position.

2. Applicant submits and affirms that all the essential aspects of the invention defined by independent Claims 1 and 15 respectively are disclosed in proper and adequate written descriptive detail; are structurally and functionally characterized by experiment and empirical data; and are

revealed in multiple illustrations and in a preferred embodiment by the Specification text. In addition, applicant has shown that the Specification text provides specific parameters, guidance and valuable insights for choosing, preparing and making embodiments of the genetically modified human microglia cell family – whenever the ordinarily skilled person in this technical field wishes to do so. Given this totality of information, guidance and insight existing within the Specification text, anyone ordinarily skilled in this art would have no need or use for a redundant recitation directed to " efficacy of in vivo treatments" as such in order to make and use applicant's defined invention.

In this regard also, applicant draws the Examiners' attention to the fact that the present invention is claimed in the alternative only as a cellular composition of matter and as a method of preparation definition. Thus, applicant's invention need not be proven as being a medically efficacious therapeutic treatment in any respect.

Furthermore, applicant respectfully submits that the manner of making the present invention is revealed in full and explicated in depth by the range and variety of the experiments and empirical data disclosed by the Specification text. Thus, the practitioner ordinarily skilled in this art could easily prepare and utilize without major difficulty many different embodiments of the genetically modified human microglia cell family in

accordance with the definition provided by independent Claims 15.

3. Applicant and his undersigned attorney also submit and maintain that the Specification text provides an abundance of description and informative details as to how to obtain and use human microglia cells which are unmodified - as well as the genetically modified human neural crest stem cells, which is the subject matter defined by the presently pending claims. Thus, so long as the ordinary practitioner can employ the disclosure to make and use these genetically modified cells, there is no legal requirement for and no factual value in other information within the written Specification of applicants' invention.

In summary, applicant his undersigned attorney respectfully submit and maintain that the Examiners have failed to comply with the proper legal standards when conducting their assessment and evaluation of the claims pending in the present application. Instead, the Examiners have wrongly demanded more details; improperly insisted upon more working examples; and peremptorily required more information – all of which would constitute only ordinary and routine experiments, and yield merely a better appreciation of in-vivo parameters; and provide, at most, an empirical showing of non-essential variables for the relevant art. None of the

Examiners' demands for such information, even if acquiesced to, would be of additional benefit to the practitioner in this field, given the quantity and quality of information and knowledge disclosed by the Specification text presently to the ordinarily skilled practitioner in the art.

For these reasons, applicant respectfully submits that the Examiners have made multiple factual and legal errors regarding the enablement requirement for the invention as presently claimed. Accordingly, on the basis of all the foregoing, applicant requests that the Examiners reconsider their position and withdraw this ground of rejection against the presently pending claims.

VI. The Rejections Under 35 U.S.C.103(a)

The Examiner has rejected the original claims under 35 U.S.C. 103(a) as being obvious over the Janabi *et al.* 1996 article, the Briers *et al.* 1994 publication, in view of the Gage *et al.* '926 patent reference. The rationale of the Examiner is stated at pages 9-10 of the instant Official Action.

Applicant, however, believes that the Examiners are factually and legally in error with regard to this issue. Applicant submits that the Examiners' recited position and views as regards the content of the relevant teachings within each of these two cited and applied references is erroneous;

and also maintains that the Examiners' manner of reliance upon the limited information provided by each of these references is inappropriate.

Initially however, a summary review of restatement of the requiste legal standards concerning non-obviousness is in order.

A. The Legal Standard For Determining Non-Obviousness:

As a matter of long established law, the proper legal basis and standard for determining obviousness under 35 U.S.C. 103 is as follows: Where applicants' claimed subject matter can be rejected as obvious in view of a single reference or a combination of prior art references, a proper analysis must consider inter alia two factors: (1) whether the prior art of record would have suggested to those of ordinary skill in the art that they should make the claimed composition or practice the claimed method; and (2) whether the prior art would also have revealed that in so making or practicing, those of ordinary skill would have a reasonable expectation of success [In re Dow Chemical Company, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988)]. Note that both the suggestion and the reasonable expectation of success must be found within the prior art references themselves and not in applicant's disclosure [In re Vaeck, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991)].

Equally important, the same inquiry must be carried out in the context of a purported "obvious modification" of the prior art information. The mere fact that the prior art might be modified in the manner suggested by the Examiners does not make that modification obvious unless the prior art itself suggested the desirability of the modification [In re Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992) and the references cited therein].

Applicant therefore respectively submits that the Examiners' stated views and conclusions in the instant Official Action do not conform to the objective legal standard required for a conclusion of obviousness.

B. The Factual Content Of the Cited And Applied References:

The Janabi et al. 1996 Article

The Janabi et. al. Article [*Neuroscience Letters 195*:105-108 (1996)] discusses the formation of a microglial cell line transformed with the large T-antigen of SV40. The use of the SV40 large T-antigen has been documented to cause significant phenotypic differences in transformed cell lines, and the current reference alludes to activation problems (the cell line appears to be constitutively activated).

However, the Janabi *et al.* text overtly points out that this particular transformed microglia cell line:

(i) is unable to grow at low density, preventing serial dilution experiments to obtain homogeneous clones;

(ii) has only 8% of cells expressing the microglial marker CD68, thereby indicating a very heterogeneous cell population;

(iii) has only 2-19% of cells able to phagocytose zymosan, whereas microglial cells are recognized as actively phagocytosing zymosan;

(iv) presents MHC II on the cell surface only after IFN-gamma stimulation; and

(v) empirically reveals a great deal of divergence among the clones.

In contrast and distinction, applicant's genetically modified human microglia cells and stable cell line presents an unique and unexpected improvement upon the Janabi *et al.* SV40 transformed cell line. This marked improvement and major advance is demonstrated by the following:

(a) Applicant's cell line is demonstrably characterized as being a stable, homogeneous human microglia cell line;

(b) Applicant's cell line is able to grow at low density;

(c) Applicant's cell line expresses CD68, as would be expected of microglial cells, actively;

(d) Applicant's cell line phagocytoses foreign particles;

(e) Applicant's cell line expresses MHC II at the cell surface even when unstimulated, as would normal human microglial cells; and, in addition

(f) Applicant's cell line is sensitive to LPS stimulation, whereas the Janabi *et al.* cells are not. This last trait is deemed to be crucial for the use of the instant cells within screening assays, a test procedure which would require microglia cells that react to challenge by stimuli such as LPS or

amyloid.

The Briers *et al.* 1994 Publication

The Briers et. al. publication [*J. Neuroimmunology 52*:153-164 (1994)] is the second prior art reference cited and applied by the Examiners. The Brier's *et al.* report describes a transfected murine cell line where the murine microglial cell lines are formed after retroviral mediated gene transfer using a v-myc containing plasmid. The outcome of this process, however, yielded cells which are markedly different from applicant's present invention.

For example, the resulting transfected murine cell lines of Briers *et al.* produced replication competent retrovirus that would severely alter the phenotypic characteristics of a cell line. This result makes impossible the obtaining of a stable, homogeneous cell line with primary microglial characteristics, as is demonstrably provided by the present invention.

Furthermore, the Briers *et al.* transfected murine cell line - characterized as adult microglial cells transfected with a v-myc encoding plasmid using lipofectin or calcium phosphate transfection protocols - reveals the following features and attributes:

(i) a poor transfection efficiency and colony generation;

(ii) a cell line with extreme heterogeneity;

(iii) a doubling time that decreased from 103 hours to 22 hours

indicating an unstable cell line prone to mutations and rearrangements;

(iv) a poor cell growth a low density;

(v) attempts at serial dilution which produced many divergent clones, and even within the sub-populations there were extreme phenotypic differences; and

(vi) results which featured incomplete characterization such as phagocytosis data and surface marker expression, results no doubt due to the cell line's heterogeneous nature.

In contrast and distinction, applicant's preferred cell line (HM06) is a product which is obtained from several initial human clones that were homogeneous in nature, and yielded human microglial cell lines whose phenotypic characteristics are the same as the original cell line. Moreover, applicants genetically modified human microglia cell lines are phenotypically and genotypically stable; and such phentypic and genotypic stability could not be expected or predicted from the published description of the Briers *et al.* v-myc transfected murine cell line, which produced only unstable and heterogenous cell lines as the reported result.

The Gage *et al.* patent reference

The Examiners also have employed the Gage et al. '926 patent [U.S. Patent No. 5,762,926] as a third prior art reference in combination with the

other two cited references. The factual relevance and informational value of this Gage *et al.* '926 patent, however, is quite limited.

The '926 patent describes the genetic modification of donor cells that are re-implanted to treat a damaged or diseased central nervous system. The genetically modified cells described by Gage *et al.* in this '926 patent are not transformed; rather, the described genetic modification involves transfection with a therapeutic gene, with the intention and goal of having the resultant protein expressed in donor cells, and in a manner which subsequently releases the protein into the inter-cellular space of the central nervous system.

Clearly, applicant's claimed invention is markedly different and remote from the cells described by the Gage *et al.* '926 patent. Applicant's human microglia cell line is transformed with a v-myc gene, whose function is to promote cell division while maintaining primary microglial cellular characteristics. The v-myc gene plays no part in the production of functional molecules encoded by recombinant products whose purpose is to effect recovery or improved function of cell in the central nervous system. Instead, it is the whole, transformed human cell, and its native microglial characteristics preserved by v-myc, which are of value and use either as cells in a screening assay, or as a whole cell agent - but which is in no way is described or predicted by a purposeful expression of a therapeutic

recombinant protein by a donor cell.

Moreover, the incidental fact that the '962 patent uses a retroviral mediated gene transfer in no way erodes the uniqueness and unforeseen characteristics and attributes empirically demonstrated and provided by applicant's HM06 cell line. To the contrary, applicant's genetically modified cells and stable cell lines alone constitute and embody the generation and maintenance of stable, transformed, and homogeneous human microglia cells.

C. The Erroneous Conclusions Of the Examiner:

As a consequence of the factual review of the three cited and applied references of record presented above, applicant respectfully submits that he has demonstrated and revealed the nature of and cause for the erroneous views and conclusions stated by the Examiner concerning the issue of non-obviousness.

Applicant maintains that the Examiners have not properly considered or appreciated the limited purpose, narrow textual context, and controlled experimental design explicitly stated within each cited and applied reference or record; have not considered the restricted scope of the empirical results reported within each cited and applied reference of record; and have overlooked the carefully worded empirical summaries and circumscribed conclusions presented within each cited and applied reference

of record. It will be recognized that applicant has made considerable effort to identify the pertinent factual differences and distinctions via their summary review of the references presented above.

Moreover, the Examiners have unfortunately wrongly chosen to extrapolate only certain specific items and details from the informational text presented by each cited and applied reference; and have misapplied the ostensible value of these extrapolated items, particularly as regards the purposes of using the v-myc gene as truly stated within the cited and applied prior art.

Applicant therefore affirms that the informational content and value taught and/or implied by the three cited and applied references of record in combination do not and can not suggest to those of ordinary skill in the relevant technical field that they should make applicant's claimed composition or practice applicant's claimed method; nor does the prior art of record collectively reveal or imply that if one attempted to make or practice applicant's claimed invention, those of ordinary skill would have a reasonable expectation of success.

For all these reasons, applicant believes that the Examiners have unknowing committed prejudicial factual and legal errors in their evaluation and stated conclusions. Applicant therefore respectfully requests that the Examiners reconsider their stated position and withdraw this ground of

rejection against the presently pending claims.

In sum, applicant submits and affirms that amended independent Claims 1 and 15 pending herein recite a subject matter and invention which is reproducible and can be made and used repeatedly, is properly enabled, and has substantial patent merit with respect to the cited and applied prior art references. Accordingly, independent Claims 1 and 15 respectively are therefore deemed to be allowable on the merits.

In addition, Claims 2-14 and 18-19 depend directly or indirectly from independent Claim 1 while Claims 16-17 depend from independent Claim 15. These dependent claims merely provide particular limitations and preferred embodiments to the unique and non-obvious invention defined therein by their antecedent independent claim. Since independent Claims 1 and 15 respectively are believed to be in condition for allowance and Claims 2-14 and 16-17 respectively depend therefrom, these dependent claims are also believed to be allowable at this time.

Lastly, applicant has addressed each basis of objection and rejection stated in the instant Official Action forthrightly and candidly. In applicant's view, each issue or controversy has been evaluated, acted upon, and resolved completely. For these reasons, applicant respectfully submits and affirms that Claims 1-19 now pending are therefore now allowable.

In view of the above discussion and detailed review, applicant believes that this case is now in condition for allowance and reconsideration is respectfully requested. The Examiners are invited to call applicant's undersigned attorney should they feel that such a telephone call would further the prosecution of the present application.

Respectfully submitted,

SEUNG U. KIM

Date: Sept. 19, 2003

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